Breast cancer screening in women at elevated risk

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CHAPTER 8
General Discussion

Summary

This thesis focuses on the optimal screening approach for three groups of women: (1) women with a *BRCA1/2* mutation; (2) women at familial risk of breast cancer (BC) without a known gene mutation; and (3) women with dense breasts. Screening programs for the general population, which usually start at ages 47-50 and consist of mammography screening every 2 or 3 years, are not sufficient for women with a known or suspected gene mutations for several reasons. Firstly, women with a *BRCA1/2* mutation are at high risk of developing BC (45%-65% cumulative risk by the age of 70) and women at familial risk (4,5) defined as having 20-50% cumulative risk which depend on the degree of family history. Further, they are more likely to develop BC at young age (median age at diagnosis: 43-47 for women with a *BRCA1/2* mutation and 48 for women at familial risk) and BC in women with a *BRCA1/2* mutation grow faster than sporadic BCs (1.5 to 3 times faster) (1-3). Therefore, dedicated screening programs for high risk populations are implemented in a hospital setting and include annual MRI starting at the age of 25 and annual mammography starting at a later age of 30 or 40 (6-8). In addition, having dense breasts is associated with false negatives in mammography since tumours can be masked by dense breast tissue. New screening modalities such as digital breast tomosynthesis (DBT), so called 3D mammography are expected to improve the detection ability of mammography in women with dense breasts. The aim of this thesis is firstly to evaluate screening accuracy of MRI and mammography in women at high risk due to a gene mutation or family history. Further, this thesis also aims to investigate the accuracy of DBT in screening women with mammographically dense breasts.

Overview of BC screening in women at high risk: a literature review

Chapter 2 provides an overview of the evidence on BC screening in women at high risk. Prospective studies supported screening with MRI as an adjunct to mammography in these women as this strategy could detect more than 90% of the BCs both for women under and above 50 years old. However, the benefit of increased survival following screening with MRI is still in doubt since there is lack of evidence based on randomized controlled trials with long follow-up and lack of evidence comparing survival benefit of mammography screening and MRI screening. Although adding MRI to mammography increased the sensitivity of screening, interval cancers still exist due to the relatively moderate sensitivity of MRI in detecting DCIS (9). Screening with annual MRI and mammography increased the number of false positives and the risk of radiation induced tumours. There is some evidence reporting the increased

the increased risk of BC due to radiation exposure before age 30 in women at high risk, however, the evidence needs to be interpreted with caution because of short follow-up time after exposure, recall bias, survival bias and selection bias (Chapter 2). Simulation studies were conducted to evaluate the cost-effectiveness of screening with MRI and mammography. There was evidence supporting screening for women with a *BRCA1/2* mutation from age 30 but no clear evidence for women at familial risk and without known mutations.

Optimization of screening: a meta-analysis

Prospective screening studies supported the added value of MRI to mammography in screening women at high risk for both women with a *BRCA1/2* mutation as well as for women at familial risk. Nevertheless, there are gaps in knowledge regarding the accuracy the appropriate start and stop age of screening stratified by the level of the risk. **Chapters 3-5** describe the results of a meta-analysis for which individual patient data from six major studies were used. In this way data from 1,951 women with a *BRCA1/2* mutation and 2,226 women with a familial increased risk could be analyzed.

The contribution of MRI to mammography in women with a BRCA1/2 mutation

At the moment there is no consensus on whether screening with MRI should also be offered to women aged 50 and over with a *BRCA1/2* mutation. Chapter 3 discusses this question using data from the meta-analysis with individual patient data. This analysis shows that the addition of MRI to mammography in the screening of women with a *BRCA1/2* mutation in women aged 50 and older increases the sensitivity of screening with the magnitude comparable to the increase in sensitivity in women younger than 50. Given this evidence, consideration should be given to continuing screening for breast cancer with MRI and mammography in women with a *BRCA1/2* mutation after the age of 50.

The contribution of mammography to MRI in women with a BRCA1/2 mutation

Although MRI sensitivity is higher than mammography, still its detection capability is not perfect. MRI has shown to be less sensitive in detecting DCIS compared to mammography (9). However, some other studies showed that the ability of MRI to detect DCIS has improved over time (10). Additional screening with mammography, especially at young age, can increase the risk of developing BC due to radiation exposure. Therefore, the discussion was raised as to whether MRI alone is sufficient in screening high risk women.

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Chapter 4 investigated whether mammography screening is still needed when the women are screened with MRI. We specifically look at the screening for BC in women younger than 50 because the disadvantages of mammography are particularly relevant to them. The results show that in women with a *BRCA1* mutation, the addition of mammography to the screening gives a slight increase (4%) of the sensitivity and a small decrease (4%) of the specificity. In *BRCA2* mutation carriers, screening with mammography is much more relevant. This shows the 12% increase in sensitivity and a small decrease in specificity (2%). However, due to the relatively small sample size in each mutation and age group, the addition of mammography to MRI did not show a statistically significant difference in sensitivity with respect to MRI alone. Therefore, it seems important for *BRCA1* and *BRCA2* mutation carriers younger than 50 to have different screening guidelines with regard to the role of mammography.

Screening of women at familial risk of breast cancer (BC) without a proven gene mutation

Chapter 5 investigated at the added value of MRI in an annual screening with mammography in women with strong family history of breast cancer but without a proven mutation. Screening with mammography had a sensitivity of 55% and a specificity of 94%. Screening with MRI alone had a sensitivity of 89% and a specificity of 83%. Combining both screening modalities increased the sensitivity to 98% and reduced the specificity to 79%. The question is whether this reduction in specificity is justified.

Intensified screening in a broader perspective

While **chapter 3-5** investigated the sensitivity and specificity of screening with MRI and mammography, chapter 6 evaluated the screening from a broader perspective. Currently, women with a *BRCA1/2* mutation are recommended for intensified screening consisting of annual MRI often starting at the age of 25 and additional mammography at the age of 30 or 40. The upper age limit of such screening varies across countries. In the Netherlands, from the age of 60, women with a *BRCA1/2* mutation are offered annual mammography alone (6). However, there are arguments to change the guidelines. The risk of developing BC still increases after the age of 60 (11,12) and the tumour growth rates are faster than sporadic BC at the same age (2,3). Additionally it was shown that mammography is not sufficient in screening women with dense breasts and women with a *BRCA1/2* mutation can still have dense breast tissue at a later age. Further, our meta-analysis proved the added value of MRI to

plus mammography considering breast density is cost-effective compared to the current guideline.

In **chapter 6**, a micro simulation model was conducted to answer this question. The model was used in previous publications and for the purpose of the present study, the input parameters were updated, and the model was validated against observed data for women with a *BRCA1/2* mutation that underwent annual or biennial mammography or annual mammography plus MRI. The model estimated comparable proportions of interval cancers and the simulated tumour size distributions were comparable to the observed data. Four scenarios were simulated: (0) annual mammography as the reference; (1) alternating MRI and mammography annually for women with dense breasts; (2) annual MRI and mammography for women with dense breasts; (3) annual MRI and mammography for all women. It was concluded that, for women with a *BRCA1* mutation and older than 60 years, screening with annual mammography plus MRI not cost-effective compared to annual mammography. Only for women with a *BRCA2* mutation and dense breasts, alternating MRI and mammography annually was cost-effective as compared to annual mammography.

Digital breast tomosynthesis in women with mammographically dense breasts

Recently, DBT and its potential implementation in BC screening has become a topic of discussion and intensive research efforts (13). Several cohort studies and systematic reviews as well as narrative reviews or expert opinions were published about using DBT with or without standard digital mammography in BC screening (14,15). **Chapter 7** reviewed the evidence regarding the ability of DBT to detect BC compared to mammography in women with dense breasts. In this review, only studies performing digital mammography as a reference were included. The evidence supported the use of DBT as it increased sensitivity, cancer detection rate and recall rate. However, the evidence was mainly reported from diagnostic studies and retrospective studies which are prone to bias. Prospective studies with long-term follow up are needed to obtain more robust evidence.

Methodological considerations

In research, study design and related biases should be considered when interpreting the results. This section discusses methodological issues which assist the interpretation of the results reported in this thesis.

Firstly, the main topic of this thesis is women with a *BRCA1/2* mutation and women with a

family history but no known mutation. Indeed, the prevalence of a *BRCA* gene in the population is only about 2% (16). Although we pooled data from six large prospective studies, the number of women with a *BRCA1/2* mutation and the number of BCs diagnosed were too small to detect a statistically significant difference in some analyses, especially when the analysis was stratified by age and *BRCA* mutation (17). Furthermore, the studies included women who were referred to genetic units. As there might be selection bias, the results are only applicable to the population referred to the genetic units.

Secondly, it was not possible to investigate the effect of family history on screening accuracy in women without a known mutation at familial risk. The data from the included studies varied in type of information on family history, depending on the specific inclusion criteria. The results from chapter 5 are for women with at least 20% life time risk. Yet, the definition of 20% lifetime risk can be heterogeneous according to the assessment tool used in the source studies. Additionally, family history is usually obtained from patient interviews and validated by medical reports. It depends on the setting whether the information given by the women can be fully or partially validated. Some information might be missed, in case of family members that do not have close contact.

Thirdly, the data for MRI in women at high risk which were evaluated in this thesis were from studies conducted since 1997. Such relatively old data might underestimate the performance of MRI and mammography in current practice. However, for a meta-analysis study this is unavoidable, and we already obtained as much current data as possible. It is however to be expected that in current practice both MRI and mammography technology have improved and hence the accuracy of the modalities has improved.

Another point to consider is that modelling studies usually simplify reality with assumptions. The model did not simulate ductal carcinoma in situ (DCIS) which accounts for about 20% of the diagnosed BCs in women with *BRCA1/2* mutation (17). Yet, the progression from DCIS to invasive is not conclusive (18) and detecting DCIS can contribute to screening benefit but also over-diagnosis (19). More concrete knowledge is needed to model the progression of DCIS and quantify related benefit and over-diagnosis. In the model, tumours were assumed to start to grow from 5mm and that was the threshold of screening detection ability. With more advanced screening techniques, this threshold could be smaller. Screening will gain more benefit when detecting small tumours.

Finally, the current evidence in screening women at high risk mostly comes from developed countries. From other parts of the world, there is very little knowledge about *BRCA* mutation

penetrance and the need for breast cancer screening. The evidence from this thesis is mostly derived from and applicable in developed countries where high risk screening program is applied.

Implication in practice and future research

Women with a BRCA1 or BRCA2 mutation should be treated differently

Since the time that the *BRCA1* and *BRCA2* mutations were discovered, studies have been carried out to explore and test their impact on the management of BC risk. So far, breast screening of women with a *BRCA1* or *BRCA2* mutation has been equal in research and in practice. However, evidence in the literature suggests that these two mutations have a different impact on the BC characteristics, leading to possible different ways of screening management. First, the penetrance curves of *BRCA1* and *BRCA2* are different. *BRAC1* mutation carriers have an increased risk of developing BC at younger ages and *BRCA2* carriers have an increased risk at older ages (1). This suggests starting screening earlier in *BRAC1* carriers and to continue screening for older ages for *BRAC2* carriers. Chapter 6 showed that screening women with a *BRCA2* mutation with MRI and mammography after the age 60 was more cost-effective compared to screening women with a *BRCA1* mutation. Second, the added value of mammography to MRI in cancer detection is different in women with a *BRCA1* and *BRCA2* mutation in different age groups as shown in **chapter 4** of this thesis. The contribution of mammography to cancer detection in women with a *BRCA2* mutation is more evident than in women with a *BRCA1* mutation especially for women younger than 40. Omitting mammography in the screening of women with a *BRCA1* mutation below the age of 40 showed a comparable benefit but a reduced risk of tumour induction (20). Starting mammography from the age of 30 was not cost-effective compared to starting at the age of 40 (20). While there is not yet a cost-effectiveness analysis available or long-term follow-up data on *BRCA2* mutation carriers comparing screening with mammography at different starting ages, from a cancer detection perspective, a sustainable number of BCs would have been missed if mammography had not been performed in women with a *BRCA2* mutation younger than 40 (**chapter 4**).

Is intensified screening justified in women with a familial risk and unknown gene mutation?

Among the diagnosed BC related to family history or a genetic predisposition, up to 90% is diagnosed in women with a family history but without a known gene mutation (21-24).

Women with a family history can have a two to four-fold risk of BC compared to women at average risk (4,5). The BC risk of these women can be assessed using different risk estimation models. Most of these models are based on the number and degree of affected relatives, and the age at cancer diagnosis (25-27). In fact, several risk estimation models are used depending on the availability in clinical practice and that are cited in the guidelines (6-8), such as BRCAPRO (27), BOADICEA (25) , and the Manchester scoring system (26). In some countries, screening outside of the general population screening program is offered to women with family history and no mutation (6-8).

Offering intensified screening to these women is challenging because it is not easy to identify the target group based on family history and to determine a suitable starting age of screening and screening modalities. Initially, the recommendations were only partially based on evidence. Prospective screening studies in women at familial risk supported screening with MRI and mammography in terms of cancer detection, however, there is a lack of evidence on long term outcomes such as survival and cost effectiveness (**chapter 2**). Additionally, there is evidence that among women with family history, only 11% develop BCs before the age of 50 (28). The cumulative life-time risk of developing BCs by the age of 50 was estimated to be 3.7% and 8% for women with at least one or two affected relatives (28). Thus, despite the increased risk, most of the BCs in women at familial risk would develop after the age of 50. In addition, some evidence suggests that the characteristics (tumour doubling time, tumour grade, nodal status, estrogen/progesterone receptor status) of BCs in women at familial risk were like sporadic cancers (2,3,29). Lastly, assessing the risk of BCs in women invited to a genetic clinic due to an affected relative is difficult since only prospective studies with life-time follow up can accurately determine the absolute risk of these women. More concrete evidence is therefore needed to evaluate the effectiveness of screening outside the general population screening for these women.

The search for new imaging techniques in BC screening for populations at increased risk of BC

Mammography has been shown to be effective in general population screening. However, mammography has its disadvantages in dense breasts. Because of lower sensitivity in dense breast, new modalities are studied for their implementation in BC screening of specific populations. MRI has been studied intensively and applied in screening women at high risk. The advantage of MRI is that its sensitivity is independent of mammographic breast density. Nevertheless, MRI is more invasive because of the use of contrast agents, has higher costs, is

less widely available and is more time consuming than mammography. The benefit of MRI in screening the high-risk population both in young and older women is presented in **chapter 3-5**. However, combining MRI with mammography has the drawback that it decreases the specificity (**chapter 3-5**). An improved MRI with high field 7.0T or combining dynamic contract enhanced MRI and diffusion weighted imaging MRI improves the specificity and provides more characteristics of the cancer (30).

Another potential modality is digital breast tomosynthesis (DBT). Most of the evidence found in literature in BC screening using DBT was performed in the general population (15). Evidence supported the value of DBT over mammography regardless of breast density in terms of cancer detection, recall rate and sensitivity (14). Yet, the evidence was heterogeneous in methodology and setting. More prospective studies with repeated screenings and long follow-up are needed to investigate the impact of DBT on screening outcomes. The disadvantage of DBT performed together with mammography is the higher radiation dose compared to mammography alone. Synthetic 2D mammography images constructed from 3D DBT data sets can be a solution for that. A review comparing the accuracy of DBT plus DM and DBT plus synthetic DM showed no significant difference between the two methods (31). Further research is needed to develop an optimal screening using new modalities, considering risk factors such as age, breast density, genetic predisposition and characteristics that can influence screening accuracy as well as evaluate the cost-effectiveness of the new modalities.

Conclusion

This thesis has provided more in-depth knowledge on the effectiveness of BC screening in women with *BRCA1/2* mutations or women without a known gene mutation at familial risk and women with dense breasts. The results are relevant and applicable mostly in developed countries where high risk screening programs are recommended.

The evidence from **chapter 3** supports the continuation of screening with annual mammography and MRI in women with a *BRCA1/2* mutation older than 50. Different screening regimes for women with a *BRCA1* and women with a *BRCA2* mutation are suggested since the contribution of mammography in cancer detection is different in women with these two types of mutations. It is striking that for women under the age of 40 with a *BRCA1* mutation, only MRI is possibly sufficient, while this does not apply to women with a *BRCA2* mutation. We support the use of annual MRI as an adjunct to mammography from a

cancer detection perspective in women without a known gene mutation at familial risk of developing BC, although there is lack of evidence on long term outcomes and from a cost-effectiveness perspective. Regarding screening after the age of 60, among different strategies using MRI, only alternating MRI and mammography annually is cost-effective compared to annual mammography for women with a *BRCA2* mutation with dense breasts. Tomosynthesis was show to improve sensitivity, cancer detection and generally reduce recall rate in women from the general population with mammographically dense breasts. However, more prospective studies with long term follow-up are needed to evaluate the efficacy of tomosynthesis in breast cancer screening.

Our results emphasize that *BRCA1* and *BRCA2* mutation carriers cannot be considered as one group. It is important to develop different screening strategies not only for the different groups of women with an increased risk of breast cancer, but also for women with dense breast tissue.

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